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A systematic review and meta-analysis of the incidence and prevalence and 30-year trend of inflammatory bowel diseases in Asia: The study protocol

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A systematic review and meta-analysis of the incidence and prevalence and 30-year trend of inflammatory bowel diseases in Asia: The study protocol

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Article summary

Strengths and Limitations of this study

- This study will provide the best evidence on Asian prevalence and incidence of UC and CD according to the different regions of Asian Continent.
- This study will provide data combining and assessing the value and causes of possible heterogeneity.
- This study has more inclusive search based on the use of thesaurus systems including Emtree and MeSh, a search in large databases such as SCOPUS, WOS, MEDLINE/PubMed, Embase, Google Scholar and ProQuest with a longer search time interval.
- Due to lack of sufficient information from some Asian countries, the final outcome may not be consistent with the actual prevalence and incidence of UC and CD.

Abstract

Introduction Inflammatory Bowel Disease including Ulcerative colitis (UC) and crohn's disease (CD) are debilitating conditions with rapidly growing in developing countries. In the absence of a comprehensive systematic review and meta-analysis with a rigorous pooled estimation of incidence and prevalence of UC and CD, we aim to conduct this study to determine Asian continent incidence and prevalence of UC and CD and also 30-year trend of these diseases.

Methods and Analysis Electronic data bases including PubMed/MEDLINE, Scopus, WoS (clarivate analytics), Embase (Embase.com) and Google Scholar and also Indian Citation Index, Korean Citation Index, Chinese Citation Index

and Iran Medex as well as large Asian cohort websites such as the PERSIAN cohort website in Iran and the Asia-Pacific Crohn's and Colitis Epidemiology Study (ACCESS) will be search based on predefined criteria, for population base cross sectional studies and baseline data report of population based cohort studies(for prevalence data) and final reports of population based cohort studies (for incidence data), involving adult patients, without language restriction from1.1.1988 and 30.12.2018. Any disagreement in the stages of screening, selecting, quality assessment and data extraction between two independent reviewers will be resolved by consensus, and if the disagreement is not resolved, the opinion of a third expert person will be used to resolve the case. The combination method will be based on methodological similarities in the included studies by the Fixed Effect Model (FEM) or the Random Effect Model (REM). Forest plot will be plotted for all the studies to show the separated and pooled incidence and prevalence and their corresponding 95% CIs. The Q-statistic test and I^2 statistic will be used to assess the statistical heterogeneity. Funnel plots will be used to assess potential reporting bias and non-significant-study effect. Begg's and Egger's tests will also be performed, and significant results (P>0.1) suggest a publication bias, in which case the 'trim and fill' method will be used. Time trends for UC and CD will be calculated with cumulative meta-analysis.

Ethics and Dissemination: Since this review will use previous published studies, it will not require the consent of the Ethics Committee. Our results will be prepared and disseminated through a peer-reviewed journal and will be presented in relevant conferences.

Key words: Inflammatory Bowel Disease; Prevalence; Systematic Review; Asia

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Background

Inflammatory Bowel Diseases (IBDs) include two chronic, non-curable, idiopathic diseases, namely Ulcerative Colitis (UC) and Crohn's Disease (CD);(1, 2), which are developed as a result of genetic(3), environmental(4) and immunologic(5) factors.

Given the absence of a histological or serologic gold standard for confirming the diagnosis of IBD and also the abundance of diseases that mimic the symptoms of this disease, IBD is diagnosed based on a series of clinical, endoscopic and histological findings(6). The two most commonly-used criteria in IBD diagnosis include the Lennard-Jones criteria(7) and Mendeloff's criteria(8).

In the present study, the definition of IBD is acceptable by either of these two criteria, and the ICD-10 diagnostic codes, which are for UC: K51.0-51.9 and CD: K50.0-50.9, are approved for the diagnosis of these diseases. Moreover, the

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incidence rate of IBD is the number of new cases of the disease in a given period of time and specific geographical area and the prevalence of IBD is the number of living IBD patients over a given period of time and in a specific geographical area.

The highest prevalence of IBD is still seen in northern industrial countries, such as North American and European countries. The prevalence of IBD appears to have stabilized in these countries at over 0.5% in the general population(9). The incidence of UC and CD is 24.3 and 29.3 per 100,000 of the population in these countries(10). These patients impose great annual costs on the health system; for example, in 2004, an estimated USD 6 billion was spent for IBD patients in the US(11). The annual costs incurred by these patients were CAD 1.2 billion in Canada and five billion Euros in Europe (12, 13).

Although the prevalence and incidence of IBD were low in Asia before the past two to three decades (due to non-diagnosis or the small number of cases), the prevalence and incidence of these diseases were severely exacerbated during this time in the countries of this continent as a result of their industrialization(14, 15).

Many studies conducted in Asia have shown the great differences in the epidemiological indices of IBDs. A study conducted in 2013 reported the incidence of IBD as 0.54 to 3.44 per 100,000 of the population(16). In South Korea, the incidence rates of UC and CD were reported as 4.6 and 3.2 per 100,000 of the population(16). From 1991 to 2005 in Japan, the prevalence of UC increased from 18.1 to 63.6 and the prevalence of CD from 5.9 to 21.1 per 100,000 of the population (17, 18). The incidence of IBD increased tenfold in South Korea over two decades(19). Despite the stabilization in its incidence in advanced countries, IBD appears to be rapidly increasing in Asia(1).

In general, the chronic nature of these diseases and their small mortality rate as well as the trend of their progression, i.e. remission and exacerbation over the

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course of the disease, and also the incidence of dysplasia and colon or rectal cancer in many of the patients(20) impose a heavy financial burden on the health system of countries in terms of both disease treatment and complications.

Examining the epidemiological indices of the prevalence and incidence of the disease and investigating the reasons for the reduction or increase in these indices over the span of some years (given the rapid trend of industrialization in Asian countries and the increasing environmental risk factors)(14) can help health policymakers calculate the burden of IBD in Asia.

To the researchers' knowledge, three systematic review studies (without any data combining, estimating and examining the reasons for heterogeneity or meta-analysis) have been conducted to date on the prevalence and incidence of IBD. A valuable research was recently carried out by C. N. Siew et al. in 2018(21) that assessed the global prevalence and incidence of IBD (*last accessed 31Dec.,2016*) by conducting a search in MEDLINE and Embase databases. The Asian part of the study examined population-based studies conducted in 19 countries of this continent. According to the findings, in East Asia, the highest and lowest incidence rates were 3.2 and 0.06 for CD and 4.6 and 0.42 for UC per 100,000 person-year and the highest and lowest prevalences were 18.6 and 1.05 for CD and 57.3 and 4.59 for UC per 100,000 of the population; in South Eastern Asia, the highest and lowest incidence rates were 0.41 and 0.14 for CD and 0.68 and 0.15 for UC per 100,000 person-year and the highest and lowest prevalence were 2.17 and 2.17 for CD and 6.67 and 6.67 for UC per 100,000 of the population; in Southern Asia, the highest and lowest incidence rates were 3.91 and 0.09 for CD and 6.02 and 0.69 for UC per 100,000 person-year and the highest and lowest prevalence were 1.2 and 1.2 for CD and 44.3 and 5.3 for UC per 100,000 of the population; in Western Asia, the highest and lowest incidence rates were 8.4 and 0.94 for CD and 6.5 and 0.77 for UC per 100,000 person-year and the highest and

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lowest prevalence were 53.1 and 50.6 for CD and 106.2 and 4.9 per 100,000 of the population. This study also investigated the temporal trend of the incidence of these diseases over the three examined decades.

Another systematic review conducted by Molodecky et al. in 2012 (*last accessed 2010*) also performed a search in MEDLINE and Embase and investigated 13 countries in Asia and the Middle East. The results showed that the incidence rate of UC ranged from 0.11 in Singapore to 6.52 in Panjab, India, per 100,000 person-years and the prevalence of UC also ranged from 4.9 in Turkey to 168 in Kibbutz, Israel, per 100,000 of the population(9). The incidence of CD ranged from 0.04 in Singapore to 5 in Kibbutz, Israel, per 100,000 person-years and its prevalence ranged from 0.88 in Japan to 67.9in Kibbutz, Israel, per 100,000 of the population. This study did not include any data combining, estimating and examining the reasons for heterogeneity or meta-analysis.

Another systematic review(22) was conducted by Lani Prideaux in 2012 (*last accessed Oct. 2011*), that examined the studies conducted in only nine Asian countries through a search in Medline (EBSCO Host) and Cochrane. The highest incidence of UC was observed in India (6 cases/10^5 person-year) and the highest incidence of CD in South Korea (5.1 cases/10^5 person-year). The highest prevalences of UC and CD were observed in Asakura, Japan (63.6 cases/10^5 person-years and 21.2 cases/10^5 of the population, respectively).

Regarding the epidemiological indices of IBD (prevalence, incidence and risk factors), two other review articles can be noted, including one by Kelvin T. Thia et al. in 2008(14) on preliminary studies in eight Asian countries and another by Jacques Cosnes et al. in 2011(10) on preliminary studies conducted in some countries (including three Asian countries).

In the present study, the priori registration in PROSPERO, data combining and assessing the value and causes of possible heterogeneity and also a more inclusive

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search based on the use of thesaurus systems including Emtree and MeSh, a search in large databases such as SCOPUS, WOS, MEDLINE/PubMed, Embase, Google Scholar and ProQuest with a longer search interval, the use of regional databases such as the Indian Citation Index, Chinese Citation Index, Korean Citation Index and IranMedex, the use of grey literature, including theses and conference papers and proceedings, and also the use of experts' views and the examination of key journals will make the present systematic review a more comprehensive examination of preliminary studies on the subjects compared to its predecessors.

Given the previous studies conducted on the prevalence and incidence of IBD, there is a north-south gradient and an east-west gradient between western countries(23) and also Asian countries(24). Nevertheless, this issue has not been specifically investigated using the dose-response method based on geographical longitude and latitude. Moreover, since westernization and industrialization appear to be risk factors for the increased incidence and prevalence of IBD(25), and since the per-capita income is one of the indicators of industrialization, the dose-response method shall be used, if possible, to investigate the relationship of this phenomena with the increased prevalence and incidence of CD or UC in Asian countries.

The present systematic review and meta-analysis was conducted to provide clinical professionals and healthcare system policymakers in Asia (the largest and most populated continent in the world with 50 countries) with the latest information about the prevalence and incidence of CD and UC, so that they can effectively and smartly deal with the challenges of the growing trend of IBDs in the next decade with the help of accurate and up-to-date information.

Objectives

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Primary Objective: The primary objective of the present systematic review and meta-analysis is to estimate the prevalence and incidence of CD and UC in adults (over age 16) in Asia (26).

Secondary Objectives:

1. Estimating the prevalence and incidence of CD and UC in Asia by age group
2. Estimating the prevalence and incidence of CD and UC in Asia by gender
3. Estimating the prevalence and incidence of CD and UC by the four geographical regions of Asia, including East Asia, Southern Asia, Southeastern Asia, and Western Asia.
4. Estimating the prevalence and incidence of CD and UC in Asia by the latitude of the study country
5. Estimating the prevalence and incidence of CD and UC in Asia by the per-capita income in the study country
6. Determining the temporal trend of the prevalence and incidence of CD and UC over the last three decades
7. Assessing the possible heterogeneity in the prevalence and incidence of CD and UC in Asia and finding its potential causes

Methods and Design

The protocol of this systematic review and meta-analysis was prepared according to the recommendations from the CRD's guideline (27)and will be reported according to the MOOS guidelines(28). The selection process of the studies will be reported according to the PRISMA-P 2015(29).

Study Eligibility Criteria

Inclusion and Exclusion Criteria

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Type of Studies

This study shall select all the population-based observational studies that have correctly (based on an acceptable definition) estimated or presented data on the prevalence and incidence (or both) of UC or CD (or both) in Asia with which these indices can be calculated. These observational studies will include population-based cross-sectional studies for estimating the prevalence and prospective population-based cohort studies (final results) for estimating the incidence. The studies should contain the numerator and denominator of the prevalence and incidence estimation fraction (to obtain the standard error of the incidence/prevalence) or else obtaining such data should be possible through correspondence with the author.

Review articles, case reports, hospital studies and case series will not be included in the presents study. Moreover, prospective population-based cohort studies (baseline data) will be used as special design to estimate the prevalence indicator.

In this study, population-based studies refer to studies conducted on a representative population of a geographical region that have used a random sampling method and have a fairly equal gender distribution (about 50% from each gender) and also an age distribution that is consistent with the age distribution in the target population (or at least one of the study age groups in the representative sample is similar to the corresponding age group in the target population).

Type of Participants

The present study will include all the preliminary studies conducted in Asian countries(26) on adult patients (male, female or both, age over 16) with CD or UC and shall exclude preliminary studies on pediatric patients (age below 16 years). Studies conducted on different Asian ethnicities or races will be included, provided that they meet the other inclusion criteria of this systematic review.

All the studies conducted outside Asia on Asian immigrates or refugees as well as those conducted in Asia on immigrants from other countries (Asian or non-Asian) will be excluded.

Disease (Outcome)

In this study, definitions of IBD, including CD or UC, based on either the Lennard Jones(7) or Mendeloff's(8) criteria are acceptable. Moreover, the ICD-10 diagnostic codes (UC: K51.0-51.9 and CD: K50.0-50.9) are approved for the diagnosis of these diseases.

All the studies using the term IBD in their title and presenting data on the prevalence or incidence (or both) of UC or CD (or both) in their text will also be included in this systematic review.

The prevalence of CD or UC: The number of patients with CD or UC at a given time (point or period of time) and a specific geographical location divided by the total population at risk in that specific location and time per 100,000 of the population.

Cumulative incidence of CD or UC:

Cumulative incidence: Number of new patients with CD or UC over a period of at least one year in a specific geographical location divided by the total population at risk in that specific location and time per 100,000 of the population.

Sampling Method and Sample Size

Sampling should have been conducted by a random method (simple random sampling, systematic random sampling, stratified random sampling and cluster random sampling, or a combination of them) in the preliminary studies that meet the eligibility criteria for this systematic review. The preliminary studies that have used a non-random sampling method (quota sampling, convenient sampling,

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purposive sampling, self-selection sampling and snowball sampling) or public calls will be excluded from this systematic review. The minimum acceptable sample size for the preliminary studies is 30.

Testing (Piloting) of the selection process

In order to examine the reliability of the interpretation of inclusion criteria and appropriate classification of the studies by two authors (MM, ARS), the pilot phase of selection process will be conducted on a sample of papers, initially. This pilot phase will also be used to verify the degree of clarity of the inclusion criteria and to ensure that the criteria are used consistently by both authors.

Search Strategy and Literature Sources

Search Strategy Components

To achieve the most inclusive search, the search strategy will only be based on the outcome component. To find the equivalent of component, thesaurus systems including Emtree and MeSH and also the free text method and the views of expert persons and also related articles and abstracts will be used. The other approaches to be used for finding relevant studies include the following:

Electronic Databases

To achieve the study objectives, searches will be carried out in the following electronic databases: PubMed/MEDLINE, Scopus, WoS (clarivate analytics), Embase (Embase.com) and Google Scholar.

Key journals and reference lists of related studies

An issue-by-issue manual search will be carried out of two journals as the key journals. The selection of these journals will be based on the analysis of the search outcome of the databases, and a search will be conducted for finding journals presenting the largest pool of sources available on the study subject based on the

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study inclusion and exclusion criteria. A manual search will also be conducted in the reference lists of the articles selected as the final candidates for quality assessment, and if an article is found in the previous review studies and systematic review studies that has been missed out in the previous search, it will be added to the final articles.

Grey Literature

To find the theses related to the study subject, electronic databases including ProQuest and Scopus will be used in addition to contacting experts.

Moreover, to obtain relevant conference papers and proceedings, electronic databases will be used in addition to the information obtained from experts. These references will be searched manually.

Others

Searching relevant internet resources

Since the present study will be conducted on Asian countries, the search will be carried out in the Indian Citation Index, Korean Citation Index, Chinese Citation Index and Iran Medex as well as large Asian cohort websites such as the PERSIAN cohort website in Iran and the Asia-Pacific Crohn's and Colitis Epidemiology Study (ACCESS).

Contacting expert persons

When contacting expert persons, they will be asked to send any relevant unpublished studies they have as well as any theses by the students working under their supervision. They will also be asked to introduce conferences related to the subject of this systematic review (in addition to the search conducted in the databases).

Date of Publication

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All the studies conducted between 1988.1.1 and 2018.12.30 and to whose results the researchers have gained access will be included.

Language of Publication

There will be no language limitations in this systematic review and meta-analysis. The studies that reach the selection stage after screening (based on their title and abstract) and meet the necessary final-stage inclusion criteria and have their full text available and have been written in a language other than English will be translated by Google Translate and then assessed for the final selection.

Constructing the Search Strategy

In order to extract the largest number of relevant studies and not miss any related articles, the only component that will be used in the search will be 'outcome (disease)' statements, as shown in Table 1. This syntax is predicted such that it provides the largest possible number of studies (in the electronic data base section) by performing the most inclusive search.

Table 1 Search strategy used in PubMed/MEDLINE from 1988 to December 2018

Number	Search terms
1	("Idiopathic Proctocolitis"[ti] OR "Ulcerative Colitis"[ti] OR "Colitis Gravis"[ti] OR ("Inflammatory Bowel Disease"[ti] AND "Ulcerative Colitis Type"[ti])OR"chronic ulcerative colitis"[ti] OR "colitis ulcerative"[ti] OR "colitis ulcerosa"[ti] OR "colitis ulcerosa

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chronic"[ti] OR (colitis[ti] AND ulcerative[ti]) OR (Colitis[ti] AND mucosal[ti]) OR (colitis[ti] AND ulcerous[ti]) OR (Colon[ti] AND "chronic ulceration"[ti]) OR "histiocytic ulcerative colitis"[ti] OR "mucosal colitis"[ti] OR "ulcerative colorectitis"[ti] OR "ulcerative procto colitis"[ti] OR "ulcerative proctocolitis"[ti] OR "ulcerous colitis"[ti])

2	("Crohn's Enteritis"[ti] OR "Regional Enteritis"[ti] OR "Crohn's Disease"[ti] OR "Crohns Disease"[ti] OR "Inflammatory Bowel Disease 1"[ti] OR "Granulomatous Enteritis"[ti] OR Ileocolitis[ti] OR "Granulomatous Colitis"[ti] OR "Terminal Ileitis"[ti] OR "Regional Ileitides"[ti] OR "Regional Ileitis"[ti] OR "cleron disease"[ti] OR "Crohn's disease"[ti] OR "Crohns disease"[ti] OR "enteritis regionalis"[ti] OR ("intestinal tract"[ti] AND "regional enteritis[ti]") OR "morbuscrohn"[ti] OR "regional enterocolitis"[ti])
3	("Inflammatory Bowel Disease"[ti] OR ("Bowel Diseases"[ti] AND Inflammatory[ti])
4	1 OR 2 OR 3
5	1988/01/01:2018/12/30[dp]
6	4 AND 5

This search strategy will be suitable for other electronic databases. Complete search syntax for PubMed and scopus are available in supplement of this protocol.

All the search stages will be recorded with full and precise details and shall be presented with the final report. All the searches carried out in the various databases will be registered in Endnote.

Study Screening and Selection

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In order to test the correct understanding of individuals from the inclusion and exclusion criteria during the screening phase, one of the contributors outside of the author's team was used. He was asked to apply the corresponding criteria to 2 output files with 100 studies (titles and abstracts). This process was performed before the protocol was registered on the PROSPERO.

The search process will carry out according to the syntaxes related to each electronic database. Then, in the screening stage, two of the authors (ARS & MM) will review the title and abstract of the studies based on a checklist prepared according to the inclusion and exclusion criteria and will find and extract the studies that they identify as related to the study subject. The studies that fail to satisfy even one of these criteria are rejected at this stage. At this stage, the studies with insufficient data in one or some of the inclusion criteria will be provisionally included in the study and a final decision will be made about them after reviewing their full text in the next stage. Then, in the selection stage, two of the authors (ARS & FE) will review the full text of the studies obtained in the screening stage and determine the final studies, independently, to enter the next stage. Any disagreement in the above two stages will be resolved by consensus, and if the disagreement is not resolved, the opinion of a third expert person(KBL) will be used to resolve the case.

Study Quality and Risk of Bias Assessment

To investigate the likelihood of a relationship between the quality of the preliminary studies and their results, the methodological quality of the included studies will be independently assessed by two of the authors (ARS & AK). Any inconsistencies will be resolved by consensus, and if no agreement is reached yet again, the case will be resolved by seeking the views of a third expert person (KBL).

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The tool to be used is a 10-item tool for assessing the methodological quality of population prevalence studies(30) and includes the following items:

Items 1 to 4 assess external validity and include the representativeness of the target population, the representativeness of the sample population (sampling frame), random selection and the non-response bias.

Items 5 to 10 assess internal validity and include data collection from the subjects or proxies, acceptable case definition, reliability and validity of the measurement tools, same mode of data collection used for all the subjects, appropriateness of the length of the shortest prevalence period, and appropriateness of the numerator(s) and denominator(s).

Data Extraction

Two authors (ARS & MM) independently complete the data extraction form for all the included studies and then discuss any disagreements to reach a consensus, and if the disagreement is not resolved, the opinion of a third expert person will determine the case. The following items will be collected and recorded in the data extraction form: Study year, publication year, first author's name, journal name, study country, design, setting, target population, sampling method, sample size, total study period, items related to the quality assessment of the study (the score of each item and the total score of the study quality), data related to the prevalence and incidence of IBDs (CD and UC), including prevalence, cumulative incidence, incidence rate, the measures included 95%CI and P-value, and also, as per the secondary objectives of this study, required data including age and gender groups, geographical region and latitude and the per-capita income of the corresponding country.

In the absence of the required statistical data in the preliminary studies, the authors will attempt to calculate them or communicate with their authors to obtain

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the data. The study will be eliminated if the author fails to respond to the communications for three times.

Data Analysis and Synthesis

The data of each of the included studies will be briefly presented in a table and shall include the first author's name, year of publication, study design and the number and characteristics of the participants. The data related to the incidence and prevalence of UC and CD will also be presented separately and based on four geographical subgroups (East Asia, South eastern Asia, Southern Asia and Western Asia).

Statistical Analysis

Pooled Analysis

The pooled incidence and prevalence for UC and CD will be calculated in this meta-analysis. The combination method will be based on methodological similarities in the included studies by the Fixed Effect Model (FEM) or the Random Effect Model (REM).

Forest plots will be plotted for all the studies to show the separated and pooled incidence and prevalence and their corresponding 95%CIs.

The software used in the present study will be Stata V.13.1 (Stata Corp, College Station, TX, USA).

Assessment of Heterogeneity

The Q-statistic test and I^2 statistic and corresponding 95%CI will be used to assess the statistical heterogeneity of the incidence and prevalence values in the included studies.

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The following references will be used as the bases for determining the degree of heterogeneity.

1- Heterogeneity values of 0-40% will be taken as 'perhaps not important', *2-* 30-60% as 'moderate heterogeneity', *3-* 50-90% as 'substantial heterogeneity' and *4-* 75-100% as 'considerable heterogeneity'. The significance level of the P-value will be <0.05 for the Q-test(31).

Subgroup Analysis

In the present study, in addition to geographical subgroups (Easter Asia, Southeastern Asia, Southern Asia and Western Asia), the studies will be divided into different subgroups and analyzed based on the geographical latitude of their corresponding countries, the per-capita income of their corresponding countries, age group, gender, method of sampling, etc.

Assessment of Publication Bias

The first strategy to deal with publication bias is performing the most inclusive search in the search stage of the study.

Also, funnel plots will be used to assess potential reporting bias and non-significant-study effect.

Begg's test and Egger's test will also be performed, and significant results (P>0.1) suggest a publication bias, in which case the 'trim and fill' method will be used.

Sensitivity Analysis

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A sensitivity analysis will also be performed in this study to assess methodological quality, design limitations, data analysis considerations, sample size and effect of missing data.

The sensitivity analysis will be based on the one-out remove method, in which the other studies are pooled and compared with each other with one of the studies left out each time.

Quality Analysis

For the quality analysis, the relationship between the methodological quality index of the preliminary studies and their results (prevalence or incidence values) will be assessed. If there are significant differences between the results of the high-quality methodological studies and the results of the poor-quality methodological studies, a combination of the studies with a minimum acceptable quality will be used as a valid and reliable estimate of the combination of these studies.

Missing Data

In the case of missing data in the final included studies, attempts will be made to access the authors' contact data and complete the missing data by corresponding with them. The lack of access to sufficient data (after sending three e-mails) shall necessarily mean the elimination of that study from the data synthesis process.

Patient and public involvement

No patient involved

Discussion

This systematic review and meta-analysis study will estimate the pooled incidence and prevalence of UC and CD in the Asian continent. It will also provide evidence of causes for high variation in reported incidence and prevalence among Asian countries. Since this study will be use of comprehensive and meticulous methods in all steps of systematic review and meta- analysis, the information obtained will be completely reliable.

Given the increasing pattern of these diseases in developing countries, the information gathered from this study can be widely used by doctors, health policy planners and custodians to allocate funds to prevention and treatment of these major diseases in Asian countries.

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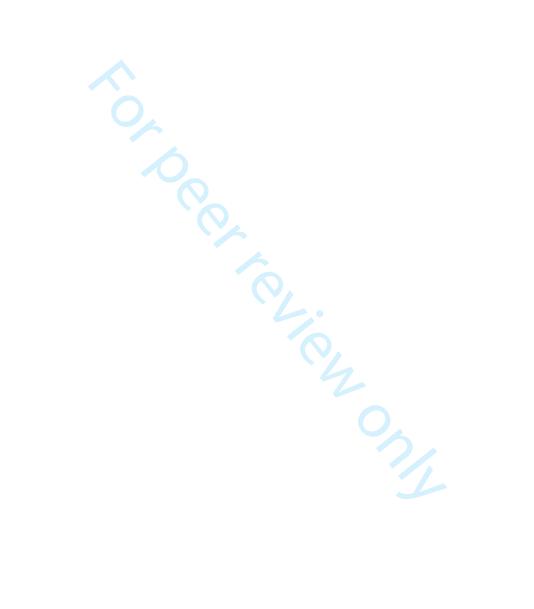
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PubMed and SCOPUS Syntax, final version

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Date:2/16/2019

("Idiopathic Proctocolitis"[ti] OR "Ulcerative Colitis"[ti] OR "Colitis Gravis"[ti] OR ("Inflammatory Bowel Disease"[ti] AND "Ulcerative Colitis Type"[ti]) OR "chronic ulcerative colitis"[ti] OR "colitis ulcerative"[ti] OR "colitis ulcerosa"[ti] OR "colitis ulcerosa chronic"[ti] OR (colitis[ti] AND ulcerative[ti]) OR (Colitis[ti] AND mucosal[ti]) OR (colitis[ti] AND ulcerous[ti]) OR (Colon[ti] AND "chronic ulceration"[ti]) OR "histiocytic ulcerative colitis"[ti] OR "mucosal colitis"[ti] OR "ulcerative colorectitis"[ti] OR "ulcerative procto colitis"[ti] OR "ulcerative proctocolitis"[ti] OR "ulcerous colitis"[ti] OR "Crohn's Enteritis"[ti] OR "Regional Enteritis"[ti] OR "Crohn's Disease"[ti] OR "Crohns Disease"[ti] OR "Inflammatory Bowel Disease 1"[ti] OR "Granulomatous Enteritis"[ti] OR Ileocolitis[ti] OR "Granulomatous Colitis"[ti] OR "Terminal Ileitis"[ti] OR "Regional Ileitides"[ti] OR "Regional Ileitis"[ti] OR "cleron disease"[ti] OR "Crohn's disease"[ti] OR "Crohns disease"[ti] OR "enteritis regionalis"[ti] OR ("intestinal tract"[ti] AND "regional enteritis[ti]") OR "morbuscrohn"[ti] OR "regional enterocolitis"[ti]) OR "Inflammatory Bowel Disease"[ti] OR ("Bowel Diseases"[ti] AND Inflammatory[ti])) AND 1988/01/01:2018/12/30[dp]

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(TITLE (*"Idiopathic Proctocolitis"*) OR TITLE (*"Ulcerative Colitis"*) OR TITLE (*"Colitis Gravis"*) OR (TITLE (*"Inflammatory Bowel Disease"*) AND TITLE (*"Ulcerative Colitis Type"*)) OR TITLE (*"Crohn's Enteritis"*) OR TITLE (*"Regional Enteritis"*) OR TITLE (*"Crohn's Disease"*) OR TITLE (*"Crohns Disease"*) OR TITLE (*"Inflammatory Bowel Disease 1"*) OR TITLE (*"Granulomatous Enteritis"*) OR TITLE (*ileocolitis*) OR TITLE (*"Granulomatous Colitis"*) OR TITLE (*"Terminal Ileitis"*) OR TITLE (*"Regional Ileitides"*) OR TITLE (*"Regional Ileitis"*) OR TITLE (*"chronic ulcerative colitis"*) OR TITLE (*"colitis ulcerative"*) OR TITLE (*"colitis ulcerosa"*) OR TITLE (*"colitis ulcerosa chronic"*) OR (TITLE (*colitis*) AND TITLE (*ulcerative*)) OR (TITLE (*colitis*) AND TITLE (*mucosal*)) OR (TITLE (*colitis*) AND TITLE (*ulcerous*)) OR (*colon[ti]* AND *chronic* AND *ulceration[ti]*) OR TITLE (*"histiocytic ulcerative colitis"*) OR TITLE (*"mucosal colitis"*) OR TITLE (*"ulcerative colorectitis"*) OR TITLE (*"ulcerative procto colitis"*) OR TITLE (*"ulcerative proctocolitis"*) OR TITLE (*"ulcerous colitis"*) OR TITLE (*"cleron disease"*) OR TITLE (*"Crohn's disease"*) OR TITLE (*"Crohns disease"*) OR TITLE (*"enteritis regionalis"*) OR (TITLE (*"intestinal tract"*) AND TITLE (*"regional enteritis"*)) OR TITLE (*"morbuscrohn"*) OR TITLE (*"regional enterocolitis"*) OR TITLE (*"Inflammatory Bowel Disease"*) OR (TITLE (*"Bowel Diseases"*) AND TITLE (*inflammatory*))) AND PUBYEAR > *1989* AND PUBYEAR < *2019*

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

"A systematic review and meta-analysis of the incidence and prevalence and 30-year trend of inflammatory bowel diseases in Asia: The study protocol"

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	21
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	21
Sponsor	5b	Provide name for the review funder and/or sponsor	-
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	-
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8-9
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	9-11
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	12-13
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could	14

			be repeated	
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review		15
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)		15-16
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators		17
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications		17
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale		11
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis		16
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised		18
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)		18-19
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)		19
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned		19
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)		19
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)		20

* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.

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A systematic review and meta-analysis of the incidence and prevalence and 30-year trend of inflammatory bowel diseases in Asia: The study protocol

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Manuscripts

A systematic review and meta-analysis of the incidence and prevalence and 30-year trend of inflammatory bowel diseases in Asia: The study protocol

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Abstract

Introduction Inflammatory Bowel Disease including Ulcerative colitis (UC) and crohn's disease (CD) and inflammatory bowel disease, type unclassified (IBDU) are debilitating conditions with rapidly growing in developing countries. In the absence of a comprehensive

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systematic review and meta-analysis with a rigorous pooled estimation of incidence and   26

prevalence of UC and CD and IBDU, we aim to conduct this study to determine Asian   27

continent incidence and prevalence of UC and CD and IBDU and also 30-year trend of these   28

diseases.   29

Methods and Analysis Electronic data bases including PubMed/MEDLINE, Scopus, WoS   30

(clarivate analytics), Embase (Embase.com) and Google Scholar and also Asian countries   31

databases, will be searched based on predefined criteria, for population base cross sectional   32

studies and baseline data and final reports of population based cohort studies, involving   33

pediatrics and adult patients, without language restriction from1.1.1988 and 30.12.2018. Any   34

disagreement in the stages of screening, selecting, quality assessment and data extraction   35

between two independent reviewers will be resolved by consensus, and if the disagreement is   36

not resolved, the opinion of a third expert person will be used to resolve the case. The   37

combination method will be based on methodological similarities in the included studies by   38

the Fixed Effect Model (FEM) or the Random Effect Model (REM). Forest plot will be   39

plotted for all the studies to show the separated and pooled incidence and prevalence and   40

their corresponding 95% CIs. The Q-statistic test and I^2 statistic will be used to assess the   41

statistical heterogeneity. Funnel plots will be used to assess potential reporting bias and non-   42

significant-study effect. Begg's and Egger's tests will also be performed, and significant   43

results (P>0.1) suggest a publication bias, in which case the 'trim and fill' method will be   44

used.Time trends for UC and CD and IBDU will be calculated with cumulative meta-   45

analysis.   46

Ethics and Dissemination: Since this review will use previous published studies, it will not   47

require the consent of the Ethics Committee. Our results will be prepared and disseminated   48

through a peer-reviewed journal and will be presented in relevant conferences.   49

Key words: Inflammatory Bowel Disease; Prevalence; Systematic Review; Asia   50

PROSPERO registration number: CRD42019131477   51

Article summary   52

Strengths and Limitations of this study   53

- This study will provide the best evidence on Asian prevalence and incidence of UC   54
   and CD and 'IBDU.   55

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- This study will provide data combining and assessing the value and causes of possible heterogeneity.

- This study has more inclusive search based on the use of thesaurus systems including Emtree and MeSh, a search in large databases such as SCOPUS, WOS, MEDLINE/PubMed, Embase, Google Scholar and ProQuest with a longer search time interval.

- Lack of strong population based studies in most countries of Asian continent, our review may not show the actual population-based prevalence and incidence of diseases under study.

- Methodological bias in primary included studies may cause uncertainty in the results of our study.

Background

Inflammatory Bowel Diseases (IBDs) include three chronic, non-curable, idiopathic diseases, namely Ulcerative Colitis (UC) and Crohn's Disease (CD) and inflammatory bowel disease, type unclassified (IBDU)(1, 2), which are developed as a result of genetic(3), environmental(4) and immunologic(5) factors.

Given the absence of a histological or serologic gold standard for confirming the diagnosis of IBD and also the abundance of diseases that mimic the symptoms of this disease, IBD is diagnosed based on a series of clinical, endoscopic and histological findings(6). The two most commonly-used criteria in IBD diagnosis include the Lennard-Jones criteria(7) and Mendeloff's criteria(8). The diagnostic criteria stated by two other references included the international multicenter scoring system of Organization Mondiale de Gastroenterologie (OMGE)(9) and the diagnosis criteria of Japanese Research Society on IBD(10) are also acceptable in this study.

In the present study, the definition of IBD is acceptable by either of these Four criteria, and the ICD-10 diagnostic codes, which are for UC: K51.0-51.9 and CD: K50.0-50.9, are approved for the diagnosis of these diseases. Inflammatory bowel disease, type unclassified (IBDU) will be define according to ICD-10 code: K52.3 and diagnostic criteria revealed by M. Guindi et al.(11) and Ouyang et al.(12). Moreover, the incidence rate of IBD is the

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number of new cases of the disease in a given period of time and specific geographical area 87
and the prevalence of IBD is the number of living IBD patients over a given period of time 88
and in a specific geographical area. 89

The highest prevalence of IBD is still seen in northern industrial countries, such as North 90
American and European countries. The prevalence of IBD appears to have stabilized in these 91
countries at over 0.5% in the general population(13). The incidence of UC and CD is 24.3 92
and 29.3 per 100,000 of the population in these countries(14). These patients impose great 93
annual costs on the health system; for example, in 2004, an estimated USD 6 billion was 94
spent for IBD patients in the US(15). The annual costs incurred by these patients were CAD 95
1.2 billion in Canada and five billion Euros in Europe (16, 17). 96

Although the prevalence and incidence of IBD were low in Asia before the past two to three 97
decades (due to non-diagnosis or the small number of cases), the prevalence and incidence of 98
these diseases were severely exacerbated during this time in the countries of this continent as 99
a result of their industrialization(18, 19). 100

Many studies conducted in Asia have shown the great differences in the epidemiological 101
indices of IBDs. A study conducted in 2013 reported the incidence of IBD as 0.54 to 3.44 per 102
100,000 of the population(20). In South Korea, the incidence rates of UC and CD were 103
reported as 4.6 and 3.2 per 100,000 of the population(20). From 1991 to 2005 in Japan, the 104
prevalence of UC increased from 18.1 to 63.6 and the prevalence of CD from 5.9 to 21.1 per 105
100,000 of the population (21, 22). The incidence of IBD increased tenfold in South Korea 106
over two decades(23). Despite the stabilization in its incidence in advanced countries, IBD 107
appears to be rapidly increasing in Asia(1). 108

In general, the chronic nature of these diseases and their small mortality rate as well as the 109
trend of their progression, i.e. remission and exacerbation over the course of the disease, and 110
also the incidence of dysplasia and colon or rectal cancer in many of the patients(24) impose 111
a heavy financial burden on the health system of countries in terms of both disease treatment 112
and complications. 113

Examining the epidemiological indices of the prevalence and incidence of the disease and 114
investigating the reasons for the reduction or increase in these indices over the span of some 115
years (given the rapid trend of industrialization in Asian countries and the increasing 116

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environmental risk factors)(18) can help health policymakers calculate the burden of IBD in Asia.

To the researchers' knowledge, three systematic review studies (without any data combining, estimating and examining the reasons for heterogeneity or meta-analysis) have been conducted to date on the prevalence and incidence of IBD. A valuable research was recently carried out by Ng et al., 2018(25) that assessed the global prevalence and incidence of IBD (*last accessed 31Dec.,2016*) by conducting a search in MEDLINE and Embase databases. The Asian part of the study examined population-based studies conducted in 19 countries of this continent. According to the findings, in East Asia, the highest and lowest incidence rates were 3.2 and 0.06 for CD and 4.6 and 0.42 for UC per 100,000 person-year and the highest and lowest prevalences were 18.6 and 1.05 for CD and 57.3 and 4.59 for UC per 100,000 of the population; in South Eastern Asia, the highest and lowest incidence rates were 0.41 and 0.14 for CD and 0.68 and 0.15 for UC per 100,000 person-year and the highest and lowest prevalence were 2.17 and 2.17 for CD and 6.67 and 6.67 for UC per 100,000 of the population; in Southern Asia, the highest and lowest incidence rates were 3.91 and 0.09 for CD and 6.02 and 0.69 for UC per 100,000 person-year and the highest and lowest prevalence were 1.2 and 1.2 for CD and 44.3 and 5.3 for UC per 100,000 of the population; in Western Asia, the highest and lowest incidence rates were 8.4 and 0.94 for CD and 6.5 and 0.77 for UC per 100,000 person-year and the highest and lowest prevalence were 53.1 and 50.6 for CD and 106.2 and 4.9 per 100,000 of the population. This study also investigated the temporal trend of the incidence of these diseases over the three examined decades.

Another systematic review conducted by Molodecky et al., 2012 (*last accessed 2010*) also performed a search in MEDLINE and Embase and investigated 13 countries in Asia and the Middle East. The results showed that the incidence rate of UC ranged from 0.11 in Singapore to 6.52 in Panjab, India, per 100,000 person-years and the prevalence of UC also ranged from 4.9 in Turkey to 168 in Kibbutz, Israel, per 100,000 of the population(13). The incidence of CD ranged from 0.04 in Singapore to 5 in Kibbutz, Israel, per 100,000 person-years and its prevalence ranged from 0.88 in Japan to 67.9in Kibbutz, Israel, per 100,000 of the population. This study did not include any data combining, estimating and examining the reasons for heterogeneity or meta-analysis.

Another systematic review(26) was conducted by LaniPrideaux., 2012 (*last accessed Oct. 2011*), that examined the studies conducted in only nine Asian countries through a search in

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Medline (EBSCO Host) and Cochrane. The highest incidence of UC was observed in India (6 cases/10^5person-year) and the highest incidence of CD in South Korea (5.1 cases/10^5 person-year). The highest prevalences of UC and CD were observed in Asakura, Japan (63.6 cases/10^5 person-years and 21.2 cases/10^5 of the population, respectively). 149 150 151 152

Regarding the epidemiological indices of IBD (prevalence, incidence and risk factors), two other review articles can be noted, including one by Kelvin T. Thia et al., 2008(18) on preliminary studies in eight Asian countries and another by Jacques Cosnes et al., 2011(14) on preliminary studies conducted in some countries (including three Asian countries). 153 154 155 156

In the present study, the priori registration in PROSPERO, review of all relevant studies regardless of age group (including pediatrics or adults), data combining and assessing the value and causes of possible heterogeneity and also a more inclusive search based on the use of thesaurus systems including Emtree and MeSh, a search in large databases such as SCOPUS, WOS, MEDLINE/PubMed, Embase, Google Scholar and ProQuest with a longer search interval, the use of regional databases such as the Indian Citation Index, Chinese Citation Index, Korean Citation Index and other five large Chinese biomedical bibliographic data bases(27) and IranMedex, the use of grey literature, including theses and conference papers and proceedings, and also the use of experts' views and the examination of key journals will make the present systematic review a more comprehensive examination of preliminary studies on the subjects compared to its predecessors. 157 158 159 160 161 162 163 164 165 166 167

Given the previous studies conducted on the prevalence and incidence of IBD, there is a north-south gradient and an east-west gradient between western countries(28) and also Asian countries(29). Nevertheless, this issue has not been specifically investigated using the dose-response method based on geographical longitude and latitude. Moreover, since westernization and industrialization appear to be risk factors for the increased incidence and prevalence of IBD(30), and since the per-capita income is one of the indicators of industrialization, the dose-response method shall be used, if possible, to investigate the relationship of this phenomena with the increased prevalence and incidence of CD or UC and IBDU in Asian countries. 168 169 170 171 172 173 174 175 176

The present systematic review and meta-analysis was conducted to provide clinical professionals and healthcare system policymakers in Asia (the largest and most populated continent in the world with 50 countries) with the latest information about the prevalence and incidence of CD and UC and IBDU, so that they can effectively and smartly deal with the 177 178 179 180

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challenges of the growing trend of IBDs in the next decade with the help of accurate and up-to-date information. 181

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Objectives 183

Primary Objective: The primary objective of the present systematic review and meta-analysis is to estimate the prevalence and incidence of CD and UC and IBDU in patients (with any ages, including pediatrics or adults) in Asia (31). 184

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Secondary Objectives: 187

1. Estimating the prevalence and incidence of CD and UC and IBDU in Asia by age group 188

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2. Estimating the prevalence and incidence of CD and UC and IBDU in Asia by gender 190

3. Estimating the prevalence and incidence of CD and UC and IBDU by the four geographical regions of Asia, including East Asia, Southern Asia, Southeastern Asia, and Western Asia. 191

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4. Estimating the prevalence and incidence of CD and UC and IBDU in Asia by the latitude of the study country 194

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5. Estimating the prevalence and incidence of CD and UC and IBDU in Asia by the per-capita income in the study country 196

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6. Determining the temporal trend of the prevalence and incidence of CD and UC and IBDU over the last three decades 198

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7. Assessing the possible heterogeneity in the prevalence and incidence of CD and UC and IBDU in Asia and finding its potential causes 200

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Methods and Design 203

The protocol of this systematic review and meta-analysis was prepared according to the recommendations from the CRD's guideline (32)and will be reported according to the MOOS guidelines(33). The selection process of the studies will be reported according to the PRISMA-P 2015(34). 204

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Study Eligibility Criteria 208

Inclusion and Exclusion Criteria 209

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Type of Studies

210

This study shall select all the population-based observational studies that have correctly (based on an acceptable definition) estimated or presented data on the prevalence and incidence (or both) of UC or CD and IBDU (or all) in Asia with which these indices can be calculated. These observational studies will include population-based cross-sectional studies for estimating the prevalence and prospective population-based cohort studies (final results) for estimating the incidence. The studies should contain the numerator and denominator of the prevalence and incidence estimation fraction (to obtain the standard error of the incidence/prevalence) or else obtaining such data should be possible through correspondence with the author.

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Review articles, case reports, hospital studies and case series will not be included in the presents study. Moreover, prospective population-based cohort studies (baseline data) will be used as special design to estimate the prevalence indicator.

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In this study, population-based studies refer to studies conducted on a representative population of a geographical region that have used a random sampling method and have a fairly equal gender distribution (about 50% from each gender) and also an age distribution that is consistent with the age distribution in the target population (or at least one of the study age groups in the representative sample is similar to the corresponding age group in the target population).

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Type of Participants

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The present study will include all the preliminary studies conducted in Asian countries(31) on patients (male, female or both, with any ages) with CD or UC and IBDU and shall exclude preliminary studies on pediatric patients (age below 16 years). Studies conducted on different Asian ethnicities or races will be included, provided that they meet the other inclusion criteria of this systematic review.

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All the studies conducted outside Asia on Asian immigrates or refugees as well as those conducted in Asia on immigrants from other countries (Asian or non-Asian) will be excluded.

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Disease (Outcome)

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In this study, definitions of IBD, including CD or UC, based on either the Lennard Jones(7) or Mendeloff's(8) criteria are acceptable. Definition of IBDU ispatients with evidence of

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clinical and endoscopic manifestations of inflammatory bowel disease affecting the colon, and no evidence of small bowel involvement, and no definitive histological or other evidences in favor of CD or UC(35). Moreover, the ICD-10 diagnostic codes (UC: K51.0-51.9 and CD: K50.0-50.9 and IBDU: K52.3) are approved for the diagnosis of these diseases.

All the studies using the term IBD in their title and presenting data on the prevalence or incidence (or both) of UC or CD or IBDU (or all) in their text will also be included in this systematic review.

The prevalence of CD or UC and IBDU: The number of patients with CD or UC or IBDU at a given time (point or period of time) and a specific geographical location divided by the total population at risk in that specific location and time per 100,000 of the population.

Cumulative incidence of CD or UC or IBDU:

Cumulative incidence: Number of new patients with CD or UC or IBDU over a period of at least one year in a specific geographical location divided by the total population at risk in that specific location and time per 100,000 of the population.

Sampling Method and Sample Size

Sampling should have been conducted by a random method (simple random sampling, systematic random sampling, stratified random sampling and cluster random sampling, or a combination of them) in the preliminary studies that meet the eligibility criteria for this systematic review. The preliminary studies that have used a non-random sampling method (quota sampling, convenient sampling, purposive sampling, self-selection sampling and snowball sampling) or public calls will be excluded from this systematic review. The minimum acceptable sample size for the preliminary studies is 30.

Testing (Piloting) of the selection process

In order to examine the reliability of the interpretation of inclusion criteria and appropriate classification of the studies by two authors (MM, ARS), the pilot phase of selection process will be conducted on a sample of papers, initially. This pilot phase will also be used to verify the degree of clarity of the inclusion criteria and to ensure that the criteria are used consistently by both authors.

Search Strategy and Literature Sources

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Search Strategy Components 269

To achieve the most inclusive search, the search strategy will only be based on the outcome 270
component. To find the equivalent of component, thesaurus systems including Emtree and 271
MeSH and also the free text method and the views of expert persons and also related articles 272
and abstracts will be used. The other approaches to be used for finding relevant studies 273
include the following: 274

Electronic Databases 275

To achieve the study objectives, searches will be carried out in the following electronic 276
databases: PubMed/MEDLINE, Scopus, WoS (clarivate analytics), Embase (Embase.com) 277
and Google Scholar. 278

Key journals and reference lists of related studies 279

An issue-by-issue manual search will be carried out of two journals as the key journals. The 280
selection of these journals will be based on the analysis of the search outcome of the 281
databases, and a search will be conducted for finding journals presenting the largest pool of 282
sources available on the study subject based on the study inclusion and exclusion criteria. A 283
manual search will also be conducted in the reference lists of the articles selected as the final 284
candidates for quality assessment, and if an article is found in the previous review studies and 285
systematic review studies that has been missed out in the previous search, it will be added to 286
the final articles. 287

Grey Literature 288

To find the theses related to the study subject, electronic databases including ProQuest and 289
Scopus will be used in addition to contacting experts. 290

Moreover, to obtain relevant conference papers and proceedings, electronic databases will be 291
used in addition to the information obtained from experts. These references will be searched 292
manually. 293

Others 294

Searching relevant internet resources 295

Since the present study will be conducted on Asian countries, the search will be carried out in the Indian Citation Index, Korean Citation Index, Chinese Citation Index and other five large Chinese biomedical bibliographic data bases(27) and Iran Medex as well as large Asian cohort websites such as the PERSIAN cohort website in Iran and the Asia-Pacific Crohn's and Colitis Epidemiology Study (ACCESS). 296 297 298 299 300

Contacting expert persons 301

When contacting expert persons, they will be asked to send any relevant unpublished studies they have as well as any theses by the students working under their supervision. They will also be asked to introduce conferences related to the subject of this systematic review (in addition to the search conducted in the databases). 302 303 304 305

Date of Publication 306

All the studies conducted between 1988.1.1 and 2018.12.30 and to whose results the researchers have gained access will be included. 307 308

Language of Publication 309

There will be no language limitations in this systematic review and meta-analysis. The studies that reach the selection stage after screening (based on their title and abstract) and meet the necessary final-stage inclusion criteria and have their full text available and have been written in a language other than English will be translated by Google Translate and recheck by official translators and then assessed for the final selection. 310 311 312 313 314

Constructing the Search Strategy 315

In order to extract the largest number of relevant studies and not miss any related articles, the only component that will be used in the search will be 'outcome (disease)' statements, as shown in Table 1. This syntax is predicted such that it provides the largest possible number of studies (in the electronic data base section) by performing the most inclusive search. 316 317 318 319

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Table 1 Search strategy used in PubMed/MEDLINE from 1988 to December 2018

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Number	Search terms
1	("Idiopathic Proctocolitis"[ti] OR "Ulcerative Colitis"[ti] OR "Colitis Gravis"[ti] OR ("Inflammatory Bowel Disease"[ti] AND "Ulcerative Colitis Type"[ti])OR"chronic ulcerative colitis"[ti] OR "colitis ulcerative"[ti] OR "colitis ulcerosa"[ti] OR "colitis ulcerosa chronic"[ti] OR (colitis[ti] AND ulcerative[ti]) OR (Colitis[ti] AND mucosal[ti]) OR (colitis[ti] AND ulcerous[ti]) OR (Colon[ti] AND "chronic ulceration"[ti]) OR "histiocytic ulcerative colitis"[ti] OR "mucosal colitis"[ti] OR "ulcerative colorectitis"[ti] OR "ulcerative procto colitis"[ti] OR "ulcerative proctocolitis"[ti] OR "ulcerous colitis"[ti])
2	("Crohn's Enteritis"[ti] OR "Regional Enteritis"[ti] OR "Crohn's Disease"[ti] OR "Crohns Disease"[ti] OR "Inflammatory Bowel Disease 1"[ti] OR "Granulomatous Enteritis"[ti] OR Ileocolitis[ti] OR "Granulomatous Colitis"[ti] OR "Terminal Ileitis"[ti] OR "Regional Ileitides"[ti] OR "Regional Ileitis"[ti] OR "cleron disease"[ti] OR "Crohn's disease"[ti] OR "Crohns disease"[ti] OR "enteritis regionalis"[ti] OR ("intestinal tract"[ti] AND "regional enteritis[ti]") OR "morbuscrohn"[ti] OR "regional enterocolitis"[ti])
3	("Inflammatory Bowel Disease"[ti] OR ("Bowel Diseases"[ti] AND Inflammatory[ti]) OR "Indeterminate colitis" OR "undetermined colitis")
4	1 OR 2 OR 3
5	1988/01/01:2018/12/30[dp]
6	4 AND 5

This search strategy will be suitable for other electronic databases. Complete search syntax for PubMed and scopus are available in supplementary file 1 of this protocol. 322 323

All the search stages will be recorded with full and precise details and shall be presented with the final report. All the searches carried out in the various databases will be registered in Endnote. 324 325 326

Study Screening and Selection 327

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In order to test the correct understanding of individuals from the inclusion and exclusion criteria during the screening phase, one of the contributors outside of the author's team was used. He was asked to apply the corresponding criteria to 2 output files with 100 studies (titles and abstracts). This process was performed before the protocol was registered on the PROSPERO.

The search process will carry out according to the syntaxes related to each electronic database. Then, in the screening stage, two of the authors (ARS & MM) will review the title and abstract of the studies based on a checklist prepared according to the inclusion and exclusion criteria and will find and extract the studies that they identify as related to the study subject. The studies that fail to satisfy even one of these criteria are rejected at this stage. The studies with insufficient data in one or some of the inclusion criteria will be provisionally included in the study and a final decision will be made about them after reviewing their full text in the next stage. Then, in the selection stage, two of the authors (ARS & FE) will review the full text of the studies obtained in the screening stage and determine the final studies, independently, to enter the next stage. Any disagreement in the above two stages will be resolved by consensus, and if the disagreement is not resolved, the opinion of a third expert person(KBL) will be used to resolve the case.

Study Quality and Risk of Bias Assessment

To investigate the likelihood of a relationship between the quality of the preliminary studies and their results, the methodological quality of the included studies will be independently assessed by two of the authors (ARS & AK). Any inconsistencies will be resolved by consensus, and if no agreement is reached yet again, the case will be resolved by seeking the views of a third expert person (KBL).

The tool to be used is a 10-item tool for assessing the methodological quality of population prevalence studies(36) and includes the following items:

Items 1 to 4 assess external validity and include the representativeness of the target population, the representativeness of the sample population (sampling frame), random selection and the non-response bias.

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Items 5 to 10 assess internal validity and include data collection from the subjects or proxies, acceptable case definition, reliability and validity of the measurement tools, same mode of data collection used for all the subjects, appropriateness of the length of the shortest prevalence period, and appropriateness of the numerator(s) and denominator(s). 357
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Data Extraction 361

Two authors (ARS & MM) independently complete the data extraction form for all the included studies and then discuss any disagreements to reach a consensus, and if the disagreement is not resolved, the opinion of a third expert person will be carried out. The following items will be collected and recorded in the data extraction form: Study year, publication year, first author's name, journal name, study country, design, setting, target population, sampling method, sample size, total study period, items related to the quality assessment of the study (the score of each item and the total score of the study quality), data related to the prevalence and incidence of IBDs (CD and UC and IBDU), including prevalence, cumulative incidence, incidence rate, the measures included 95%CI and P-value, and also, as per the secondary objectives of this study, required data including age and gender groups, geographical region and latitude and the per-capita income of the corresponding country. 362
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In the absence of the required statistical data in the preliminary studies, the authors will attempt to calculate them or communicate with their authors to obtain the data. The study will be eliminated if the author fails to respond to the communications for three times. 374
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Data Analysis and Synthesis 378

The data of each of the included studies will be briefly presented in a table and shall include the first author's name, year of publication, study design and the number and characteristics of the participants. The data related to the incidence and prevalence of UC and CD and IBDU will also be presented separately and based on four geographical subgroups (East Asia, South eastern Asia, Southern Asia and Western Asia). 379
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Statistical Analysis 384

Pooled Analysis 385

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The pooled incidence and prevalence for UC and CD and IBDU will be calculated in this meta-analysis. The combination method will be based on methodological similarities in the included studies by the Fixed Effect Model (FEM) or the Random Effect Model (REM). 386 387 388

Forest plots will be plotted for all the studies to show the separated and pooled incidence and prevalence and their corresponding 95%CIs. 389 390

The software used in the present study will be Stata V.13.1 (Stata Corp, College Station, TX, USA). 391 392

Assessment of Heterogeneity 393

The Q-statistic test and I^2 statistic and corresponding 95%CI will be used to assess the statistical heterogeneity of the incidence and prevalence values in the included studies. 394 395

The following references will be used as the bases for determining the degree of heterogeneity. 396 397

1-Heterogeneity values of 0-40% will be taken as 'perhaps not important',2- 30-60% as 'moderate heterogeneity', 3- 50-90% as 'substantial heterogeneity' and 4- 75-100% as 'considerable heterogeneity'. The significance level of the P-value will be <0.05 for the Q-test(37). 398 399 400 401

Dose-Response Relationship Evaluation: 402

According to previous studies(28, 29, 38), latitude of the countries and their national income per capita (as a proxy of socioeconomic status), may be related to the prevalence or incidence of inflammatory bowel disease. We will calculate these quantitative variables for all Asian countries which have included studies in our systematic review. Then we will change these quantitative variables into three or more categories. Using command DRMETA in STATA software, we will calculate the dose-response relationship between these two variables and the incidence and prevalence of inflammatory bowel disease. Obviously, this calculation is the way to show the relationship of the two variables with the diseases under study and future studies should be consider and evaluate the mediating variables in the disease process. 403 404 405 406 407 408 409 410 411

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Temporal trend analysis 413

Temporal trends in incidence rate and prevalence during time, will calculate for included studies using join point regression program, Version 4.5.0.1 (Statistical Research and 414 415

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Applications Branch, National Cancer Institute). This program will use the annual prevalence   416

and incidence rate, and identify the years in which changes in the trend of inflammatory   417

bowel disease were occurred (join points), and then with expontiating beta-coefficients of   418

Poisson regression and subtracting 1, will calculate the annual percentage change (APC) of   419

aforementioned indicators with a 95% CI, between the trend points. The program will also   420

calculate the Average Annual Percentage Change (AAPC) for the entire study period(39, 40).   421

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Subgroup Analysis   425

In the present study, in addition to geographical subgroups (Easter Asia, Southeastern Asia,   426

Southern Asia and Western Asia), the studies will be divided into different subgroups and   427

analyzed based on the geographical latitude of their corresponding countries, the per-capita   428

income of their corresponding countries, age group, gender, method of sampling, etc.   429

Assessment of Publication Bias   430

The first strategy to deal with publication bias is performing the most inclusive search in the   431

search stage of the study.   432

Also, funnel plots will be used to assess potential reporting bias and non-significant-study   433

effect.   434

Begg's test and Egger's test will also be performed, and significant results (P>0.1) suggest a   435

publication bias, in which case the 'trim and fill' method will be used.   436

Sensitivity Analysis   437

A sensitivity analysis will also be performed in this study to assess methodological quality,   438

design limitations, data analysis considerations, sample size and effect of missing data.   439

The sensitivity analysis will be based on the one-out remove method, in which the other   440

studies are pooled and compared with each other with one of the studies left out each time.   441

Quality Analysis   442

For the quality analysis, the relationship between the methodological quality index of the preliminary studies and their results (prevalence or incidence values) will be assessed. If there are significant differences between the results of the high-quality methodological studies and the results of the poor-quality methodological studies, a combination of the studies with a minimum acceptable quality will be used as a valid and reliable estimate of the combination of these studies.

Missing Data

In the case of missing data in the final included studies, attempts will be made to access the authors' contact data and complete the missing data by corresponding with them. The lack of access to sufficient data (after sending three e-mails) shall necessarily mean the elimination of that study from the data synthesis process.

Patient and public involvement

No patient involved

Discussion

This systematic review and meta-analysis study will estimate the pooled incidence and prevalence of UC and CD and IBDU in the Asian continent. It will also provide evidence of causes for high variation in reported incidence and prevalence among Asian countries. Since this study will be use of comprehensive and meticulous methods in all steps of systematic review and meta- analysis, the information obtained will be completely reliable.

Some of the most important limitations of our future study are: high level of heterogeneity in prevalence studies because of relation of those studies to the times and places, lack of strong population based studies in most countries of Asian continent and probable methodological bias in included primary studies.

Given the increasing pattern of these diseases in developing countries, the information gathered from this study can be widely used by doctors, health policy planners and custodians to allocate funds to prevention and treatment of these major diseases in Asian countries.

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PubMed and SCOPUS Syntax, final version

46301 article in pubmed

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("Idiopathic Proctocolitis"[ti] OR "Ulcerative Colitis"[ti] OR "Colitis Gravis"[ti] OR ("Inflammatory Bowel Disease"[ti] AND "Ulcerative Colitis Type"[ti]) OR "chronic ulcerative colitis"[ti] OR "colitis ulcerative"[ti] OR "colitis ulcerosa"[ti] OR "colitis ulcerosa chronic"[ti] OR (colitis[ti] AND ulcerative[ti]) OR (Colitis[ti] AND mucosal[ti]) OR (colitis[ti] AND ulcerous[ti]) OR (Colon[ti] AND "chronic ulceration"[ti]) OR "histiocytic ulcerative colitis"[ti] OR "mucosal colitis"[ti] OR "ulcerative colorectitis"[ti] OR "ulcerative procto colitis"[ti] OR "ulcerative proctocolitis"[ti] OR "ulcerous colitis"[ti] OR "Crohn's Enteritis"[ti] OR "Regional Enteritis"[ti] OR "Crohn's Disease"[ti] OR "Crohns Disease"[ti] OR "Inflammatory Bowel Disease 1"[ti] OR "Granulomatous Enteritis"[ti] OR Ileocolitis[ti] OR "Granulomatous Colitis"[ti] OR "Terminal Ileitis"[ti] OR "Regional Ileitides"[ti] OR "Regional Ileitis"[ti] OR "cleron disease"[ti] OR "Crohn's disease"[ti] OR "Crohns disease"[ti] OR "enteritis regionalis"[ti] OR ("intestinal tract"[ti] AND "regional enteritis[ti]") OR "morbuscrohn"[ti] OR "regional enterocolitis"[ti]) OR "Inflammatory Bowel Disease"[ti] OR ("Bowel Diseases"[ti] AND Inflammatory[ti])) AND 1988/01/01:2018/12/30[dp]

SCOPUS, 54,287, 2/16/2019

(TITLE (*"Idiopathic Proctocolitis"*) OR TITLE (*"Ulcerative Colitis"*) OR TITLE (*"Colitis Gravis"*) OR (TITLE (*"Inflammatory Bowel Disease"*) AND TITLE (*"Ulcerative Colitis Type"*)) OR TITLE (*"Crohn's Enteritis"*) OR TITLE (*"Regional Enteritis"*) OR TITLE (*"Crohn's Disease"*) OR TITLE (*"Crohns Disease"*) OR TITLE (*"Inflammatory Bowel Disease 1"*) OR TITLE (*"Granulomatous Enteritis"*) OR TITLE (*ileocolitis*) OR TITLE (*"Granulomatous Colitis"*) OR TITLE (*"Terminal Ileitis"*) OR TITLE (*"Regional Ileitides"*) OR TITLE (*"Regional Ileitis"*) OR TITLE (*"chronic ulcerative colitis"*) OR TITLE (*"colitis ulcerative"*) OR TITLE (*"colitis ulcerosa"*) OR TITLE (*"colitis ulcerosa chronic"*) OR (TITLE (*colitis*) AND TITLE (*ulcerative*)) OR (TITLE (*colitis*) AND TITLE (*mucosal*)) OR (TITLE (*colitis*) AND TITLE (*ulcerous*)) OR (*colon[ti]* AND *chronic* AND *ulceration[ti]*) OR TITLE (*"histiocytic ulcerative colitis"*) OR TITLE (*"mucosal colitis"*) OR TITLE (*"ulcerative colorectitis"*) OR TITLE (*"ulcerative procto colitis"*) OR TITLE (*"ulcerative proctocolitis"*) OR TITLE (*"ulcerous colitis"*) OR TITLE (*"cleron disease"*) OR TITLE (*"Crohn's disease"*) OR TITLE (*"Crohns disease"*) OR TITLE (*"enteritis regionalis"*) OR (TITLE (*"intestinal tract"*) AND TITLE (*"regional enteritis"*)) OR TITLE (*"morbuscrohn"*) OR TITLE (*"regional enterocolitis"*) OR TITLE (*"Inflammatory Bowel Disease"*) OR (TITLE (*"Bowel Diseases"*) AND TITLE (*inflammatory*))) AND PUBYEAR > *1989* AND PUBYEAR < *2019*

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

"A systematic review and meta-analysis of the incidence and prevalence and 30-year trend of inflammatory bowel diseases in Asia: The study protocol"

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	21
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	21
Sponsor	5b	Provide name for the review funder and/or sponsor	-
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	-
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8-9
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	9-11
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	12-13
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could	14

			be repeated	
Study records:				
Data management	11a		Describe the mechanism(s) that will be used to manage records and data throughout the review	15
Selection process	11b		State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	15-16
Data collection process	11c		Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	17
Data items	12		List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	17
Outcomes and prioritization	13		List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	11
Risk of bias in individual studies	14		Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	16
Data synthesis	15a		Describe criteria under which study data will be quantitatively synthesised	18
	15b		If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	18-19
	15c		Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	19
	15d		If quantitative synthesis is not appropriate, describe the type of summary planned	19
Meta-bias(es)	16		Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	19
Confidence in cumulative evidence	17		Describe how the strength of the body of evidence will be assessed (such as GRADE)	20

* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

A systematic review and meta-analysis of the incidence and prevalence and 30-year trend of inflammatory bowel diseases in Asia: A study protocol

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A systematic review and meta-analysis of the incidence and prevalence and 30-year trend of inflammatory bowel diseases in Asia: A study protocol

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Abstract

Introduction: Inflammatory bowel diseases, including Ulcerative Colitis (UC), Crohn's disease (CD) and Inflammatory Bowel Disease type Unclassified (IBDU) are debilitating conditions that are rapidly growing in developing countries. Given the absence of a

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comprehensive systematic review and meta-analysis containing a rigorous pooled estimate of incidence and prevalence of UC, CD and IBDU, this study was conducted to determine the incidence and prevalence of these conditions in Asia and their 30-year trend.

Methods and Analysis: Based on pre-defined criteria, electronic databases, including PubMed/MEDLINE, Scopus, WoS (Clarivate Analytics), Embase and Google Scholar, and some databases pertaining to Asian countries will be searched for population-based cross-sectional studies and the baseline data and final reports of population-based cohort studies involving pediatric and adult patients, with no language restrictions, from Jan. 1, 1988, to Dec. 30, 2018. Any disagreement in the stages of screening, selecting, quality assessment and data extraction between the two independent reviewers will be resolved by consensus, and if the disagreement is not resolved, a third expert opinion will be sought. The combination method will be used based on methodological similarities in the included studies by the Fixed Effect Model (FEM) or the Random Effect Model (REM). Forest plots will be plotted for all the studies to show the separated and pooled incidence and prevalence and their corresponding 95% CIs. The Q-statistic test and I^2 statistic will be used to assess statistical heterogeneity. Funnel plots will be used to assess potential reporting bias and non-significant study effect. Begg's and Egger's tests will also be performed, and significant results (P>0.1) shall suggest a publication bias, in which case the 'trim and fill' method will be used. The time trends for UC, CD and IBDU will be calculated using a cumulative meta-analysis.

Ethics and Dissemination: Since this review will use previous published studies, it will not require the consent of an Ethics Committee. The results will be prepared and disseminated through a peer-reviewed journal and will be presented in relevant conferences.

Keywords: Inflammatory Bowel Disease; Prevalence; Systematic Review; Asia

PROSPERO registration number**:** CRD42019131477

Article summary

Strengths and limitations

1. This study will provide evidence on the Asian prevalence and incidence of UC, CD and IBDU.

2. This study will combine data and assess the value and causes of possible heterogeneity.

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3.   This study uses an inclusive search based on thesaurus systems, including Emtree and MeSh, and carries out its search in large databases, such as SCOPUS, WOS, MEDLINE/PubMed, Embase, Google Scholar and ProQuest, with a long time range.

4.   Given the lack of strong population-based studies in most countries in Asia, this review may not show the actual population-based prevalence and incidence of the diseases under study.

5.   Methodological biases in the primary studies included may cause uncertainty in the results of the present study.

Background

Inflammatory Bowel Diseases (IBDs) include three chronic, non-curable and idiopathic diseases, namely Ulcerative Colitis (UC), Crohn's Disease (CD) and Inflammatory Bowel Disease type Unclassified (IBDU) (1, 2), which are developed as a result of genetic (3), environmental (4) and immunologic (5) factors.

Given the absence of a histological or serological gold standard for confirming the diagnosis of IBD and also the abundance of diseases that mimic the symptoms of this disease, IBD is diagnosed based on a series of clinical, endoscopic and histological findings (6). The two most commonly-used criteria in IBD diagnosis include the Lennard-Jones criteria (7) and the Mendeloff criteria (8). The diagnostic criteria stated in two other references, including the international multicenter scoring system of the Organization Mondiale de Gastroenterologie (OMGE) (9) and the diagnosis criteria of the Japanese Research Society on IBD (10), are also acceptable in this study.

A definition of IBD by either of these four criteria is acceptable in this study, and the ICD-10 diagnostic codes, i.e. K51.0-51.9 for UC and K50.0-50.9 for CD, are approved for the diagnosis of these diseases. IBDU will be defined according to the ICD-10 code: K52.3 and the diagnostic criteria revealed by M. Guindi et al. (11) and Ouyang et al. (12). Moreover, the incidence rate of IBD is the number of new cases of the disease over a given period of time in a specific geographical area, and the prevalence of IBD is the number of living IBD patients over a given period of time in a specific geographical area.

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The highest prevalence of IBD is still seen in northern industrial countries, such as North American and European countries. The prevalence of IBD appears to have stabilized in these countries at over 0.5% in the general population (13). The incidence of UC and CD is 24.3 and 29.3 per 100,000 of the population in these countries (14). These patients impose great annual costs on the health system; for example, in 2004, an estimated USD 6 billion was spent on IBD patients in the US (15). The annual costs incurred by these patients were CAD 1.2 billion in Canada and EUR 5 billion in Europe (16, 17).

Although the prevalence and incidence of IBD were low in Asia before the past two to three decades (due to non-diagnosis or the small number of cases), the prevalence and incidence of these diseases were severely exacerbated in Asian countries after this time as a result of their industrialization (18, 19).

Many studies conducted in Asia have shown great differences in the epidemiological indices of IBDs. A study conducted in 2013 reported the incidence of IBD as 0.54 to 3.44 per 100,000 of the population (20). In South Korea, the incidence rates of UC and CD were reported as 4.6 and 3.2 per 100,000 of the population (20). From 1991 to 2005 in Japan, the prevalence of UC increased from 18.1 to 63.6 and the prevalence of CD from 5.9 to 21.1 per 100,000 of the population (21, 22). The incidence of IBD increased tenfold in South Korea over two decades (23). Despite the stabilization in its incidence in advanced countries, IBD appears to be rapidly growing in Asia (1).

In general, the chronic nature of these diseases, their small mortality rate, their trend of progression, i.e. remission and exacerbation over the course of the disease, and the comorbidity of dysplasia and colon or rectal cancer in many of the patients (24) impose a heavy financial burden on the health system of countries in terms of both disease treatment and complications.

Examining the epidemiological indices of the prevalence and incidence of the disease and investigating the reasons for the reduction or increase in these indices over the years (given the rapid trend of industrialization in Asian countries and the increasing environmental risk factors) can help health policymakers calculate the burden of IBD in Asia (18).

To the researchers' knowledge, three systematic reviews have been conducted to date on the prevalence and incidence of IBD, but without data combining, making estimates, examining the reasons for heterogeneity or conducting a meta-analysis. A valuable research was recently carried out by Ng et al. in 2018 (25) that assessed the global prevalence and incidence of IBD

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(*last accessed 31 Dec.,2016*) by conducting a search in MEDLINE and Embase. The Asian part of the study examined population-based studies conducted in 19 countries of this continent. According to the findings, in East Asia, the highest and lowest incidence rates were 3.2 and 0.06 for CD and 4.6 and 0.42 for UC per 100,000 person-year and the highest and lowest prevalence rates were 18.6 and 1.05 for CD and 57.3 and 4.59 for UC per 100,000 of the population; in South Eastern Asia, the highest and lowest incidence rates were 0.41 and 0.14 for CD and 0.68 and 0.15 for UC per 100,000 person-year and the highest and lowest prevalence rates were 2.17 and 2.17 for CD and 6.67 and 6.67 for UC per 100,000 of the population; in Southern Asia, the highest and lowest incidence rates were 3.91 and 0.09 for CD and 6.02 and 0.69 for UC per 100,000 person-year and the highest and lowest prevalence rates were 1.2 and 1.2 for CD and 44.3 and 5.3 for UC per 100,000 of the population; in Western Asia, the highest and lowest incidence rates were 8.4 and 0.94 for CD and 6.5 and 0.77 for UC per 100,000 person-year and the highest and lowest prevalence rates were 53.1 and 50.6 for CD and 106.2 and 4.9 per 100,000 of the population. This study also investigated the temporal trend of the incidence of these diseases over the three examined decades.

Another systematic review conducted by Molodecky et al., 2012 (*last accessed 2010*) also performed a search in MEDLINE and Embase and investigated 13 countries in Asia and the Middle East. The results showed that the incidence rate of UC ranged from 0.11 in Singapore to 6.52 in Panjab, India, per 100,000 person-years and the prevalence of UC also ranged from 4.9 in Turkey to 168 in Kibbutz, Israel, per 100,000 of the population (13). The incidence of CD ranged from 0.04 in Singapore to 5 in Kibbutz, Israel, per 100,000 person-years and its prevalence ranged from 0.88 in Japan to 67.9 in Kibbutz, Israel, per 100,000 of the population. This study did not entail data combining, making estimates, examining the reasons for heterogeneity or conducting a meta-analysis.

Another systematic review (26), conducted by Lani Prideaux. in 2012 (*last accessed Oct. 2011*), examined studies conducted in only nine Asian countries through a search in Medline (EBSCO Host) and Cochrane. The highest incidence of UC was observed in India (6 cases/10^5 person-year) and the highest incidence of CD in South Korea (5.1 cases/10^5 person-year). The highest prevalence rates of UC and CD were observed in Asakura, Japan (63.6 cases/10^5 person-years and 21.2 cases/10^5 of the population, respectively).

Two other review articles were found on the epidemiological indices of IBD (prevalence, incidence and risk factors), including one by Kelvin T. Thia et al. in 2008 (18) on preliminary

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studies in eight Asian countries, and another by Jacques Cosnes et al. in 2011 (14) on preliminary studies conducted in some countries (including three Asian countries). 149
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The present systematic review will be a more comprehensive examination of the preliminary studies on the subject in question compared to its predecessors because of its priori registration in PROSPERO, review of all the relevant studies regardless of age group (including pediatrics or adults), data combining, assessment of the value and causes of possible heterogeneity, inclusive search based on the use of thesaurus systems (Emtree and MeSh), search in large databases (SCOPUS, WOS, MEDLINE/PubMed, Embase, Google Scholar and ProQuest) with a longer time range, use of regional databases (Indian Citation Index, Chinese Citation Index, Korean Citation Index and five other large Chinese biomedical bibliographic databases (27) and IranMedex), use of gray literature (theses and conference papers and proceedings) and also use of experts' views and examination of key journals. 151
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Based on the results of previous studies conducted on the prevalence and incidence of IBD, there is a north-south gradient and an east-west gradient between western countries (28) and Asian countries in this respect (19). Nevertheless, this issue has not been specifically investigated using the dose-response method based on geographical longitude and latitude. Moreover, since westernization and industrialization appear to be risk factors for the increased incidence and prevalence of IBD (29), and since the per-capita income is one of the indicators of industrialization, the dose-response method shall be used, if possible, to investigate the relationship of this phenomena with the increased prevalence and incidence of CD, UC and IBDU in Asian countries. 161
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The present systematic review and meta-analysis was conducted to provide clinical professionals and healthcare system policymakers in Asia (the largest and most populated continent in the world with 50 countries) with the latest information about the prevalence and incidence of CD, UC and IBDU, so that these groups can more effectively deal with the challenges of the growing trend of IBDs over the next decade. 170
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Objectives 175

Primary Objective: The primary objective of the present systematic review and meta-analysis is to estimate the prevalence and incidence of CD, UC and IBDU in patients (of any age, including pediatrics or adults) in Asia (30). According to United Nations, Department of Economic and Social Affairs, Statistics Division, the Asian Continent consists of five 176
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geographical subdivisions, including Central Asia (Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan and Uzbekistan), Eastern Asia (China, China; Hong Kong Special Administrative Region, China; Macao Special Administrative Region, Democratic People's Republic of Korea, Japan, Mongolia, Republic of Korea), South-Eastern Asia (Brunei Darussalam, Cambodia, Indonesia, Lao People's Democratic Republic, Malaysia, Myanmar, Philippines, Singapore, Thailand, Timor-Leste and Vietnam), Southern Asia (Afghanistan, Bangladesh, Bhutan, India, Iran (Islamic Republic of), Maldives, Nepal, Pakistan and Sri Lanka) and Western Asia (Armenia, Azerbaijan, Bahrain, Cyprus, Georgia, Iraq, Israel, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, State of Palestine, Syrian Arab Republic, Turkey, United Arab Emirates and Yemen).

Secondary Objectives:

1. Estimating the prevalence and incidence of CD, UC and IBDU in Asia by age group.
2. Estimating the prevalence and incidence of CD, UC and IBDU in Asia by gender.
3. Estimating the prevalence and incidence of CD, UC and IBDU by the five geographical regions of Asia, including Central Asia, East Asia, Southern Asia, South-Eastern Asia and Western Asia.
4. Estimating the prevalence and incidence of CD, UC and IBDU in Asia by the latitude of the study country.
5. Estimating the prevalence and incidence of CD, UC and IBDU in Asia by the per-capita income of the study country.
6. Determining the temporal trend of the prevalence and incidence of CD, UC and IBDU over the last three decades.
7. Assessing potential heterogeneity in the prevalence and incidence of CD, UC and IBDU in Asia and finding its potential causes.

Methods and Design

The protocol for this systematic review and meta-analysis was prepared according to the Center for Reviews and Dissemination (CRD) guidelines (31) and will be reported according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (32). The

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selection process of the studies will be reported according to the Preferred Reporting Items for Systematic review and Meta-Analysis- Protocols (PRISMA-P) 2015 (33). 210

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Study Eligibility Criteria 212

Inclusion and Exclusion Criteria 213

Types of Studies 214

This study shall select all the population-based observational studies that have correctly (based 215
on an acceptable definition) estimated or presented data on the prevalence and incidence (or 216
both) of UC, CD or IBDU (or all) in Asia with which these indices can be calculated. These 217
observational studies will include population-based cross-sectional studies for estimating the 218
prevalence, and prospective, population-based, cohort studies (final results) for estimating the 219
incidence. The studies should contain the numerator and denominator of the prevalence and 220
incidence estimation fraction (to obtain the standard error of the incidence/prevalence); if not, 221
these data will be gathered through correspondence with the author. 222

Review articles, case reports, hospital studies and case series will not be included in the 223
presents study. Moreover, prospective, population-based, cohort studies (baseline data) will be 224
used as a special design to estimate the prevalence indicator. 225

In this study, population-based studies refer to studies conducted on a representative population 226
of a geographical region that have used a random sampling method and have a fairly equal 227
gender distribution (about 50% from each gender) and also an age distribution that is consistent 228
with the age distribution in the target population (or at least one of the study age groups in the 229
representative sample should be similar to the corresponding age group in the target 230
population). 231

Types of Participants 232

The present study will include all the preliminary studies conducted in Asian countries (30) on 233
patients (male, female or both, at any age) with CD, UC or IBDU. Studies conducted on 234
different Asian ethnicities or races will be included, provided that they meet the other inclusion 235
criteria of this systematic review. 236

All the studies conducted outside Asia on Asian immigrates or refugees as well as those 237
conducted in Asia on immigrants from other countries (Asian or non-Asian) will be excluded. 238

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Disease (Outcome)

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This study accepts definitions of IBD (including CD or UC) based on either the Lennard Jones (7) or Mendeloff (8) criteria. IBDU is defined as clinical and endoscopic manifestations of inflammatory bowel disease affecting the colon without showing any evidence of small bowel involvement and with no definitive histological or other types of evidence in favor of CD or UC (34). Moreover, the ICD-10 diagnostic codes (UC: K51.0-51.9, CD: K50.0-50.9 and IBDU: K52.3) are approved for the diagnosis of these diseases.

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All the studies using the term IBD in their title and presenting data on the prevalence or incidence (or both) of UC, CD or IBDU (or all) in their text will also be included in this systematic review.

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The prevalence of CD, UC or IBDU: The number of patients with CD, UC or IBDU at a given time (point or period of time) in a specific geographical location divided by the total population at risk in that specific location and time per 100,000 of the population.

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Cumulative incidence of CD, UC or IBDU:

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Cumulative incidence: Number of new patients with CD, UC or IBDU over a period of at least one year in a specific geographical location divided by the total population at risk in that specific location and time per 100,000 of the population.

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Sampling Method and Sample Size

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Sampling should have been conducted by a random method (simple random sampling, systematic random sampling, stratified random sampling and cluster random sampling, or a combination of them) in the preliminary studies that meet the eligibility criteria for this systematic review. The preliminary studies that have used a non-random sampling method (quota sampling, convenient sampling, purposive sampling, self-selection sampling and snowball sampling) or public calls will be excluded from this systematic review. The minimum acceptable sample size for the preliminary studies is 30(35).

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Selection Process Testing (Pilot)

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In order to examine the two authors' (MM and ARS) reliability of interpretation of the inclusion criteria and their appropriate classification of the studies, the pilot phase of the selection process will be initially conducted on a sample of papers. This pilot phase will also be used to verify

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the degree of clarity of the inclusion criteria and to ensure that the criteria are used consistently by both authors. 268

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Search Strategy and Literature Sources 270

Search Strategy Components 271

To achieve the most inclusive search, the search strategy will only be based on the outcome 272 component. To find the equivalent of component, thesaurus systems, including Emtree and 273 MeSH, the free text method, the views of experts and also related articles and abstracts will be 274 used. The other approaches to be used for finding relevant studies include the following: 275

Electronic Database Search 276

To achieve the study objectives, searches will be carried out in the following electronic 277 databases: PubMed/MEDLINE, Scopus, WoS (Clarivate Analytics), Embase (Embase.com) 278 and Google Scholar. 279

Search in Key Journals and the Reference Lists of Related Studies 280

An issue-by-issue manual search will be carried out of two key journals. The journals will be 281 selected based on the analysis of the search outcome of the databases, and a search will be 282 conducted for finding journals presenting the largest pool of sources available on the study 283 subject based on the study inclusion and exclusion criteria. A manual search will also be 284 conducted in the reference lists of the articles selected as the final candidates for quality 285 assessment, and if an article is found in the previous systematic or non-systematic reviews that 286 has been missed out, it will be added to the final articles. 287

Gray Literature 288

To find the theses related to the study subject, electronic databases including ProQuest and 289 Scopus will be used in addition to contacting the experts. 290

Moreover, to obtain relevant conference papers and proceedings, electronic databases will be 291 used in addition to the expert information obtained. These references will be searched 292 manually. 293

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Searching Relevant Internet Resources
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Since the present study will be conducted on Asian countries, the search will be carried out in
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the Indian Citation Index, Korean Citation Index, Chinese Citation Index and five other large
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Chinese biomedical bibliographic databases (27) and Iran Medex as well as large Asian cohort
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websites, such as the PERSIAN cohort website in Iran and the Asia-Pacific Crohn's and Colitis
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Epidemiology Study (ACCESS).
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Contacting the Experts
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When contacting experts, they will be asked to send any relevant unpublished studies they have
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as well as any theses by the students working under their supervision. They will also be asked
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to introduce conferences related to the subject of this systematic review (in addition to the
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search conducted in the databases).
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Date of Publication
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All the studies conducted between Jan. 1, 1988, and Dec. 30, 2018, to whose results the
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researchers have gained access, will be included.
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Language of Publication
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There will be no language limitations in this systematic review and meta-analysis. The studies
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that reach the selection stage after screening (based on their title and abstract) and meet the
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necessary final-stage inclusion criteria and have their full text available and have been written
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in a language other than English will be translated by Google Translate and rechecked by
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official translators and then assessed for the final selection.
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Constructing the Search Strategy
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In order to extract the largest number of relevant studies and not miss any related articles, the
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only component that will be used in the search will be 'outcome (disease)' statements, as shown
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in Table 1. This syntax is predicted such that it provides the largest possible number of studies
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(in the electronic data base section) by performing the most inclusive search.
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Table 1 The search strategy used in PubMed/MEDLINE from 1988 to December 2018

Number	Search terms
1	("Idiopathic Proctocolitis"[ti] OR "Ulcerative Colitis"[ti] OR "Colitis Gravis"[ti] OR ("Inflammatory Bowel Disease"[ti] AND "Ulcerative Colitis Type"[ti])OR"chronic ulcerative colitis"[ti] OR "colitis ulcerative"[ti] OR "colitis ulcerosa"[ti] OR "colitis ulcerosa chronic"[ti] OR (colitis[ti] AND ulcerative[ti]) OR (Colitis[ti] AND mucosal[ti]) OR (colitis[ti] AND ulcerous[ti]) OR (Colon[ti] AND "chronic ulceration"[ti]) OR "histiocytic ulcerative colitis"[ti] OR "mucosal colitis"[ti] OR "ulcerative colorectitis"[ti] OR "ulcerative procto colitis"[ti] OR "ulcerative proctocolitis"[ti] OR "ulcerous colitis"[ti])
2	("Crohn's Enteritis"[ti] OR "Regional Enteritis"[ti] OR "Crohn's Disease"[ti] OR "Crohns Disease"[ti] OR "Inflammatory Bowel Disease 1"[ti] OR "Granulomatous Enteritis"[ti] OR Ileocolitis[ti] OR "Granulomatous Colitis"[ti] OR "Terminal Ileitis"[ti] OR "Regional Ileitides"[ti] OR "Regional Ileitis"[ti] OR "cleron disease"[ti] OR "Crohn's disease"[ti] OR "Crohns disease"[ti] OR "enteritis regionalis"[ti] OR ("intestinal tract"[ti] AND "regional enteritis[ti]") OR "morbuscrohn"[ti] OR "regional enterocolitis"[ti])
3	("Inflammatory Bowel Disease"[ti] OR ("Bowel Diseases"[ti] AND Inflammatory[ti]) OR "Indeterminate colitis" OR "undetermined colitis")
4	1 OR 2 OR 3
5	1988/01/01:2018/12/30[dp]
6	4 AND 5

This search strategy will be suitable for other electronic databases. Appendix 1 of this protocol presents the researchers' complete search syntax for PubMed and Scopus.

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All the search stages will be recorded with full details and shall be presented with the final report. All the searches carried out in the various databases will be registered in Endnote.

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Study Screening and Selection

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In order to test the subjects' correct understanding of the inclusion and exclusion criteria during the screening phase, one of the contributors outside the author's team was employed. He was asked to apply the corresponding criteria to two output files with 100 studies (titles and abstracts). This process was performed before the protocol was registered on the PROSPERO. 327 328 329 330

The search process will be carried out according to the syntaxes related to each electronic database. Then, in the screening stage, two of the authors (ARS and MM) will review the title and abstract of the studies based on a checklist prepared according to the inclusion and exclusion criteria and will find and extract the studies that they identify as related to the study subject. The studies that fail to satisfy even one of these criteria are rejected at this stage. The studies with insufficient data in one or some of the inclusion criteria will be provisionally included in the study and a final decision will be made about them after reviewing their full text in the next stage. Then, in the selection stage, two of the authors (ARS and FE) will review the full text of the studies obtained in the screening stage and determine the final studies, independently, to enter the next stage. Any disagreement in the above two stages will be resolved by consensus, and if the disagreement is not resolved, the opinion of a third expert (KBL) will be used to resolve the case. 331 332 333 334 335 336 337 338 339 340 341 342

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Study Quality and Risk of Bias Assessment 344

To investigate the likelihood of a relationship between the quality of the preliminary studies and their results, the methodological quality of the included studies will be independently assessed by two of the authors (ARS and AK). Any inconsistencies will be resolved by consensus, and if no agreement is reached yet again, the case will be resolved by seeking the views of a third expert (KBL). 345 346 347 348 349

The tool to be used is a 10-item tool for assessing the methodological quality of population prevalence studies (36) and includes the following items: 350 351

Items 1 to 4 assess external validity and include the representativeness of the target population, the representativeness of the sample population (sampling frame), random selection and the non-response bias. 352 353 354

Items 5 to 10 assess internal validity and include data collection from the subjects or proxies, acceptable case definition, reliability and validity of the measurement tools, same mode of data 355 356

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collection used for all the subjects, appropriateness of the length of the shortest prevalence period, and appropriateness of the numerator(s) and denominator(s). 357

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Data Extraction 359

Two authors (ARS and MM) will independently complete the data extraction form for all the included studies and then discuss any disagreements to reach a consensus, and if the disagreement is not resolved, the opinion of a third expert will be sought. The following items will be collected and recorded in the data extraction form: Study year, publication year, first author's name, journal name, study country, design, setting, target population, sampling method, sample size, total study period, items related to the quality assessment of the study (the score of each item and the total score of the study quality), data related to the prevalence and incidence of IBDs (CD, UC and IBDU, including prevalence, cumulative incidence and incidence rate, based on the measured 95% CI and P-value) and also, as per the secondary objectives of this study, age and gender groups, geographical region and latitude and the per-capita income of the corresponding country. 360 361 362 363 364 365 366 367 368 369 370

In the absence of the required statistical data in the preliminary studies, the authors will attempt to calculate them or communicate with their authors to obtain the data. The study will be eliminated if the author fails to respond to the communications for three times. 371 372 373

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Data Analysis and Synthesis 375

The data of each of the included studies will be briefly presented in a table and shall include the first author's name, year of publication, study design and the number and characteristics of the participants. The data related to the incidence and prevalence of UC, CD and IBDU will also be presented separately based on the five geographical subgroups (Central Asia, East Asia, South-Eastern Asia, Southern Asia and Western Asia). 376 377 378 379 380

Statistical Analysis 381

Pooled Analysis 382

The pooled incidence and prevalence for UC, CD and IBDU will be calculated in this meta-analysis. The combination method will be based on methodological similarities in the included studies by the Fixed Effect Model (FEM) or the Random Effect Model (REM). 383 384 385

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Forest plots will be plotted for all the studies to show the separated and pooled incidence and prevalence and their corresponding 95% CI's. 386
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The software used in the present study will be Stata V.13.1 (Stata Corp, College Station, TX, USA). 388
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Assessment of Heterogeneity 390

The Q-statistic test and I^2 statistic and their corresponding 95% CI's will be used to assess the statistical heterogeneity of the incidence and prevalence values in the included studies. 391
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The following references will be used as the bases for determining the degree of heterogeneity. 393

1. Heterogeneity values of 0-40% will be taken as 'perhaps not important'; 2. Heterogeneity values of 30-60% as 'moderate heterogeneity'; 3. Heterogeneity values of 50-90% as 'substantial heterogeneity'; and 4. Heterogeneity values of 75-100% as 'considerable heterogeneity'. The level of statistical significance will be set at P<0.05 for the Q-test (37). 394
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Dose-Response Relationship Evaluation 398

According to previous studies (28, 38, 39), the latitude of countries and their national income per capita (as a proxy of socioeconomic status) may be somehow associated with the prevalence or incidence of IBDs in them. This review study will calculate these quantitative variables for all the Asian countries that have studies included in this systematic review. The quantitative variables will then be divided into three or more categories. Using the DRMETA command in STATA software, the dose-response relationship between these two variables and the incidence and prevalence of IBDs will be calculated. The result will show the relationship of the two variables with the diseases under study, and future studies should also consider evaluating mediating variables when examining a disease process. 399
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Temporal Trend Analysis 409

The temporal trends in incidence and prevalence over time will be calculated for the included studies using Join point Regression Program, Version 4.5.0.1 (Statistical Research and Applications Branch, National Cancer Institute). This program will use the annual prevalence and incidence rates and identify the years in which changes have occurred in the trend of IBDs (join points), and then, using exponentiating beta-coefficients of Poisson regression and 410
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subtracting 1, the Annual Percentage Change (APC) of these indicators will be calculated
between the trend points at a 95% CI. The program will also calculate the Average Annual
Percentage Change (AAPC) for the entire study period (40, 41).

Subgroup Analysis

In the present study, in addition to geographical subgroups (Central Asia, Easter Asia, South-
Eastern Asia, Southern Asia and Western Asia), the studies will be divided into different
subgroups and analyzed based on the geographical latitude of their corresponding countries,
the per-capita income of their corresponding countries, age group, gender, method of
sampling, etc.

Assessment of Publication Bias

The first strategy to deal with publication bias is performing the most inclusive search in the
search stage of the study.

Also, funnel plots will be used to assess potential reporting bias and non-significant-study
effect.

Begg's test and Egger's test will also be performed, and significant results (P>0.1) shall
suggest a publication bias, in which case the 'trim and fill' method will be used.

Sensitivity Analysis

A sensitivity analysis will also be performed in this study to assess methodological quality,
design limitations, data analysis considerations, sample size and effect of missing data.

The sensitivity analysis will be based on the one-out remove method, in which the other
studies are pooled and compared with each other with one of the studies left out each time.

Quality Analysis

For the quality analysis, the relationship between the methodological quality index of the
preliminary studies and their results (prevalence or incidence values) will be assessed. If there

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are significant differences between the results of the high-quality methodological studies and the results of the poor-quality methodological studies, a combination of the studies with a minimum acceptable quality will be used as a valid and reliable estimate of the combination of these studies.

Missing Data

In the case of missing data in the final included studies, attempts will be made to access the authors' contact data and complete the missing data by corresponding with them. The lack of access to sufficient data (after sending three e-mails) shall necessarily mean the elimination of that study from the data synthesis process.

Patient and public involvement: No patients will be involved in this study.

Discussion

This systematic review and meta-analysis study will estimate the pooled incidence and prevalence of UC, CD and IBDU in the Asian continent. It will also provide evidence of the causes for the high variation in the reported incidence and prevalence of these diseases in Asian countries. Since this study will use comprehensive and meticulous methods in all the steps of the systematic review and meta-analysis, the information obtained will be completely reliable.

Some of the most important limitations of the future study will be: The high level of heterogeneity in prevalence studies because of the dependence of these studies on time and place, the lack of strong population-based studies in most countries of the Asian continent and probable methodological bias in including the primary studies.

Given the increasing pattern of these diseases in developing countries, the information gathered from this study can be widely used by physicians, health policymakers and custodians to allocate funds to the prevention and treatment of these major diseases in Asian countries.

Author Contributions: ARS is the guarantor of this study. All the authors contributed to the conception and design of the protocol as follows. ARS worked on the topic refinement, formulation of research question, review design, study selection forms, data extraction sheets

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and plan of analysis and wrote the protocol; ARS also designed the search strategy under the 471
supervision of AK, KBL, MM and FE. KBL, MM and AK contributed to the topic 472
refinement, formulation of research question, review design and plan of analysis and gave 473
critical feedback on the intellectual content of the draft protocol. KBL, AK, FE and MM 474
reviewed the manuscript for feedback. MM will review the articles and take care of the data 475
extraction step along with ARS. AK, MM and FE will take care of database management and 476
carry out the literature search/handle the bibliography. As the senior author, KBL supervised 477
the preparation of the study protocol and addressed the reviewers' comments. All the authors 478
read and approved the final manuscript. 479

Conflicts of Interest: None declared. 485

Patient Consent: Not required. 486

Provenance and Peer Review: Not commissioned; externally peer reviewed. 487

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PubMed and SCOPUS Syntax, final version

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("Idiopathic Proctocolitis"[ti] OR "Ulcerative Colitis"[ti] OR "Colitis Gravis"[ti] OR ("Inflammatory Bowel Disease"[ti] AND "Ulcerative Colitis Type"[ti]) OR "chronic ulcerative colitis"[ti] OR "colitis ulcerative"[ti] OR "colitis ulcerosa"[ti] OR "colitis ulcerosa chronic"[ti] OR (colitis[ti] AND ulcerative[ti]) OR (Colitis[ti] AND mucosal[ti]) OR (colitis[ti] AND ulcerous[ti]) OR (Colon[ti] AND "chronic ulceration"[ti]) OR "histiocytic ulcerative colitis"[ti] OR "mucosal colitis"[ti] OR "ulcerative colorectitis"[ti] OR "ulcerative procto colitis"[ti] OR "ulcerative proctocolitis"[ti] OR "ulcerous colitis"[ti] OR "Crohn's Enteritis"[ti] OR "Regional Enteritis"[ti] OR "Crohn's Disease"[ti] OR "Crohns Disease"[ti] OR "Inflammatory Bowel Disease 1"[ti] OR "Granulomatous Enteritis"[ti] OR Ileocolitis[ti] OR "Granulomatous Colitis"[ti] OR "Terminal Ileitis"[ti] OR "Regional Ileitides"[ti] OR "Regional Ileitis"[ti] OR "cleron disease"[ti] OR "Crohn's disease"[ti] OR "Crohns disease"[ti] OR "enteritis regionalis"[ti] OR ("intestinal tract"[ti] AND "regional enteritis[ti]") OR "morbuscrohn"[ti] OR "regional enterocolitis"[ti]) OR "Inflammatory Bowel Disease"[ti] OR ("Bowel Diseases"[ti] AND Inflammatory[ti])) AND 1988/01/01:2018/12/30[dp]

SCOPUS, 54,287, 2/16/2019

(TITLE (*"Idiopathic Proctocolitis"*) OR TITLE (*"Ulcerative Colitis"*) OR TITLE (*"Colitis Gravis"*) OR (TITLE (*"Inflammatory Bowel Disease"*) AND TITLE (*"Ulcerative Colitis Type"*)) OR TITLE (*"Crohn's Enteritis"*) OR TITLE (*"Regional Enteritis"*) OR TITLE (*"Crohn's Disease"*) OR TITLE (*"Crohns Disease"*) OR TITLE (*"Inflammatory Bowel Disease 1"*) OR TITLE (*"Granulomatous Enteritis"*) OR TITLE (*ileocolitis*) OR TITLE (*"Granulomatous Colitis"*) OR TITLE (*"Terminal Ileitis"*) OR TITLE (*"Regional Ileitides"*) OR TITLE (*"Regional Ileitis"*) OR TITLE (*"chronic ulcerative colitis"*) OR TITLE (*"colitis ulcerative"*) OR TITLE (*"colitis ulcerosa"*) OR TITLE (*"colitis ulcerosa chronic"*) OR (TITLE (*colitis*) AND TITLE (*ulcerative*)) OR (TITLE (*colitis*) AND TITLE (*mucosal*)) OR (TITLE (*colitis*) AND TITLE (*ulcerous*)) OR (*colon[ti]* AND *chronic* AND *ulceration[ti]*) OR TITLE (*"histiocytic ulcerative colitis"*) OR TITLE (*"mucosal colitis"*) OR TITLE (*"ulcerative colorectitis"*) OR TITLE (*"ulcerative procto colitis"*) OR TITLE (*"ulcerative proctocolitis"*) OR TITLE (*"ulcerous colitis"*) OR TITLE (*"cleron disease"*) OR TITLE (*"Crohn's disease"*) OR TITLE (*"Crohns disease"*) OR TITLE (*"enteritis regionalis"*) OR (TITLE (*"intestinal tract"*) AND TITLE (*"regional enteritis"*)) OR TITLE (*"morbuscrohn"*) OR TITLE (*"regional enterocolitis"*) OR TITLE (*"Inflammatory Bowel Disease"*) OR (TITLE (*"Bowel Diseases"*) AND TITLE (*inflammatory*))) AND PUBYEAR > *1989* AND PUBYEAR < *2019*

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

"A systematic review and meta-analysis of the incidence and prevalence and 30-year trend of inflammatory bowel diseases in Asia: The study protocol"

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	21
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	21
Sponsor	5b	Provide name for the review funder and/or sponsor	-
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	-
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8-9
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	9-11
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	12-13
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could	14

			be repeated	
Study records:				
Data management	11a		Describe the mechanism(s) that will be used to manage records and data throughout the review	15
Selection process	11b		State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	15-16
Data collection process	11c		Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	17
Data items	12		List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	17
Outcomes and prioritization	13		List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	11
Risk of bias in individual studies	14		Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	16
Data synthesis	15a		Describe criteria under which study data will be quantitatively synthesised	18
	15b		If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	18-19
	15c		Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	19
	15d		If quantitative synthesis is not appropriate, describe the type of summary planned	19
Meta-bias(es)	16		Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	19
Confidence in cumulative evidence	17		Describe how the strength of the body of evidence will be assessed (such as GRADE)	20

* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.

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